DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

January 10, 2007

Dear ANDA Holder/Applicant:

We are writing to you as the sponsor of an approved abbreviated new drug application(s) (ANDAs) supported by bioequivalence studies in which the bioanalytical analysis was conducted by MDS Pharma Services (MDS) at the St. Laurent (Montreal) and Blainville sites in Quebec, Canada.

FDA has conducted several comprehensive inspections of bioequivalence studies conducted by MDS since 2000. The findings of these inspections raise significant concerns about the validity of the reported results of these analytical studies conducted in support of drug applications for marketing. Our findings from these inspections include, but are not limited to, the following:

- Failure to conduct a systematic and thorough evaluation to identify and correct sources of contamination.
- Failure to investigate anomalous results.
- Lack of assay reproducibility between original and repeat results.
- Assay accuracy not assured under the conditions of sample processing.
- Biased exclusion of study data resulting in the acceptance of failed runs.
- Failure to demonstrate the accuracy of analytical methods with appropriate validation experiments and documentation.

As a result of these findings, MDS agreed to conduct an audit of data from all its bioequivalence studies generated from January 2000 to December 2004. However, FDA identified significant deficiencies with the MDS audit during its most recent inspection. Thus, serious questions remain about the validity of bioequivalence data generated by MDS in studies during this time period that have not been inspected by FDA, including the studies you have submitted in support of your applications. In view of these findings, FDA is informing holders of approved ANDA(s) of these issues and would like to know what steps are being taken by you to assure the accuracy of data submitted in these applications and confirm the validity of MDS's analytical studies that were conducted from January 2000 through December 2004 and subsequently submitted to the FDA. Accordingly, with respect to these studies submitted in your applications, we recommend

that within 6 months of the date of this letter you do one of the following, in order of FDA preference:

1. Repeat the bioequivalence studies.

2. Re-assay the samples at a different bioanalytical facility. For this option, the integrity of the original samples must be demonstrated for the frozen storage period.

3. Commission a scientific audit by a qualified independent expert, who is knowledgeable in the area of bioequivalence studies and bioanalytical data, and selected by your company rather than by MDS, to verify the results obtained by MDS.

In addition, because one of the agency's significant findings for the inspected MDS studies was the presence of anomalous results, we are recommending for all of the above options that the blood/plasma level results obtained in the studies be compared to any published literature or other relevant information that is publicly available. If you are unable to complete one of these options within the recommended six month time frame, please inform us of the reason(s) and your estimated time of completion.

If you choose to conduct an audit, we recommend that the completed audit reports be maintained at your site. If the audit finds the study acceptable, we recommend that you submit a certification to your application that formally attests in writing to the validity of the results obtained by MDS upon which your application relies. If the audit finds the study to be unacceptable, we recommend that you either repeat the bioequivalence study and submit the information within 6 months of the completed audit or withdraw the application. Please note that these audits would also be subject to validity assessment by the agency upon submission. The audit criteria provided below includes, but is not limited to, examples of areas that should be evaluated.

- The audit criteria for reviewing pre-study validation data should address whether accuracy and stability were demonstrated with appropriate validation experiments and documentation, and under the conditions of sample processing used for the analysis of samples from study subjects.

- The audit criteria for reviewing the results of the bioequivalence studies should address whether anomalous results were investigated and issues related to contamination were identified and corrected. It should also determine if a comparison of all available original and repeat results demonstrated assay reproducibility, and whether analytical runs were accepted in accordance with established procedures and without bias.

The new bioequivalence data or the re-analysis of the existing data should be submitted as a supplement to your approved application. Please find attached the list of your approved applications with studies conducted at MDS during the specified time period.

As noted, we are recommending that the results of the bioequivalence studies, re-assays, or audits be submitted to your application within 6 months of the date of this letter. As you probably know,

the Agency uses its publication Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book) to provide the public with the most current information with respect to approved drug products and therapeutic equivalence. Therefore, if the information is not submitted or if the new information does not support a finding of bioavailability/bioequivalence, the FDA will consider downgrading the therapeutic equivalence evaluation of approved applications in the Orange Book from an "AB" to a "BX" rating. See Orange Book, Section 1.10 (describing the change from an "AB" to a "BX" rating "as a result of new information raising a significant question as to bioequivalence").

If you have any questions regarding this letter, please contact Cecelia Parise, Regulatory Policy Advisor to the Director, Office of Generic Drugs, at 240-276-9310.

Sincerely,

/s/ "Gary J. Buehler"

Gary J. Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research